NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2003

PLAN FOR HIV-RELATED RESEARCH

VII: MICROBICIDES

PREPARED BY THE OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Microbicides

SCIENTIFIC ISSUES

NEED AND RATIONALE

There is a real need and urgency to expand the range of preventive interventions for HIV transmission. It is not known when a safe and effective vaccine will be developed, and even when such a vaccine will become available, it is acknowledged that a vaccine will be one of the many approaches to preventing HIV. In the interim, nonvaccine prevention methods are needed that can be controlled by women to prevent HIV transmission. Microbicides, defined as antimicrobial products that can be applied topically for the prevention of sexually transmitted diseases (STDs), including HIV, may offer one of the most promising preventive interventions that could be safe, effective, inexpensive, readily available, and widely acceptable. Topical microbicides used alone or in combination with physical barriers can be used by HIV-infected individuals to prevent transmission to their partners and by uninfected individuals to protect themselves from acquiring HIV. Furthermore, microbicides could also be used as a mode of protection by men who have sex with men (MSM). Thus, a consensus has emerged across the STD and AIDS research communities that microbicide development presents an important opportunity and challenge that stands in need of greater investment.

The impact of AIDS on developing nations of Africa, Asia, Latin America, the Caribbean, and the former Soviet Union countries is staggering, with even greater potential to come. In these countries, heterosexual transmission is the predominant mode of HIV spread. Recent data indicate that worldwide there are now almost equal numbers of men and women infected

with HIV. In sub-Saharan Africa, the area hardest hit by the pandemic, the United Nations Joint Programme on AIDS (UNAIDS) and the World Health Organization (WHO) estimated that more women than men were living with HIV/AIDS at the end of 1999: 12.2 million women and 10.1 million men between the ages of 15 and 49. Of the more than 16,000 estimated new infections every day, half occur in young persons between the ages of 15 and 24, and teenage girls are disproportionately affected compared to boys. Attitudes, beliefs, and taboos surrounding sex, the status of women and children, and the source and etiology of AIDS also complicate attempts to control transmission and provide appropriate prevention and treatment.

In the United States, the HIV/AIDS epidemic continues to evolve. Although the incidence of new AIDS cases has declined, attributed largely to expanded use of new antiretroviral therapies, the decline in death rates observed in the late 1990s has leveled off. Further, according to the Centers for Disease Control and Prevention (CDC), the rate of new HIV infections has been constant, meaning that the overall epidemic is continuing to expand. In fact, HIV infection rates are continuing to climb in a number of subpopulation groups, including women, racial and ethnic minorities, young homosexual men, and people over 50 years of age. These data forebode an epidemic of even greater magnitude in the coming years. In the United States, more than 30 percent of newly reported HIV cases diagnosed are occurring in women, according to the most recent data collected by the CDC. As in the rest of the world, the majority of these reported HIV infections among U.S. women result from heterosexual transmission, and the data suggest that younger women are disproportionately at risk for acquiring HIV.

The number of new infections worldwide shows that, although consistent and correct use of condoms can provide excellent protection against HIV transmission, for a number of different reasons, men are reluctant to use condoms. Prevention options for women to protect themselves from acquisition of HIV and STDs remain minimal. Prevention programs that promote condom use require a certain level of communication and negotiation between partners. But for many women in the United States, in other developed countries and in developing countries, negotiating safe sex that includes the use of condoms may not be possible. Women, especially in developing countries, are economically, culturally, and socially marginalized. As a result, male/female power relations are not balanced, and women become infected because they cannot insist on condom use or cannot protect themselves from nonconsensual, coercive sex.

CHALLENGES FOR MICROBICIDE DEVELOPMENT

In spite of the enormous potential of microbicides, there is no definitive data or proof of concept as yet establishing that any product applied topically in humans can prevent HIV infection. Although microbicides have been under development for more than a decade, there is a general perception that there has been insufficient progress in this area. Many factors may have and continue to contribute to this lack of progress, including important scientific challenges presented by aspects of microbicides research and development.

Microbicide research requires a complex multidisciplinary and multisectoral approach by teams of scientists with expertise ranging from the biomedical to the behavioral and social sciences, to experts in clinical trials and drug discovery and development. Because of uncertainty about the potential market, microbicide research has attracted involvement of only a minimal number of small pharmaceutical and biotechnology companies with very limited funding. No major pharmaceutical company is investing significant resources in this area. Microbicide research requires huge and complex efficacy and effectiveness studies that must be conducted in areas with high HIV incidence rates; such rates occur predominantly in developing countries where the research infrastructure is underdeveloped.

The ethical obligation to provide counseling and availability of condoms to the study subjects adds to the complexity and size of the trials. Very few Phase III efficacy trials have been completed, and these have not yielded promising results. The clinical trial of COL-1492 (a gel containing 52.5 mg of nonoxynol 9 [N9]) was recently halted until the data are fully analyzed. Preliminary data analysis found more HIV seroconversion in women who received the COL-1492 than among those using placebos. Thus, it can be inferred from the data that N9 did not protect against HIV infection and may actually have facilitated HIV transmission.

This study highlighted two additional challenges in microbicides development: (1) the identification of an appropriate placebo that does not have antimicrobial activity or protective value per se and (2) the limited ability of *in vitro* and animal models to predict clinical efficacy. The disappointing results of the COL-1492 study have not been viewed by the research community as a complete setback for microbicide development. To the contrary, the results of the study have created a sense of urgency to accelerate the pace and to increase our efforts to study newer products, particularly those that even at high concentrations appear to have no effect on the structural integrity and function of the cervico-vaginal or rectal epithelium.

MICROBICIDE RESEARCH AT NIH

The NIH AIDS prevention research agenda has made a high priority the development of chemical and physical barriers that can be used intravaginally and intrarectally to inactivate and block HIV and other STDs. The NIH has a comprehensive research program that includes the screening, discovery, development, preclinical *in vitro* and *in vivo* testing, and clinical evaluation of compounds that have the potential for microbial agents with both spermicidal and nonspermicidal activity. NIH closely collaborates with academia and industry to identify and explore new and existing compounds for potential antimicrobial and/or spermicidal activity as potential topical microbicidal agents.

Animal model testing and toxicity studies of potential lead compounds are conducted through NIH-sponsored contracts before these agents are considered for clinical trials. NIH also supports Phase I, II, and III clinical trials of potential microbicides in both domestic and international settings. Currently four categories of compounds are undergoing thorough testing: cell/pathogen surface disruptive agents that kill or inactivate viruses and pathogens (N9-containing existing spermicides and new formulations, benzalkonium chloride, chlorexidine, SDS, and C31G); inhibitors of viral binding and fusion/entry into susceptible cells (sulfated/sulfonated polymers, cyanovirin, and gp41 fusion inhibitors); enhancers of normal vaginal defense mechanisms (lactobacilli, acid buffers, peroxidases, antibiotic peptides, and monoclonal antibodies); and inhibitors of HIV replication (antiretroviral drugs such as nucleoside and reverse transcriptase inhibitors). Some of these products are nonspecific and have both spermicidal and antimicrobial activity against HIV and other pathogens and some specifically interfere with HIV attachment and entry or the ability of the virus to replicate once it has entered a susceptible cell. Topical microbicides for HIV prevention would not need to be inherently spermicidal but could be formulated with or without spermicidal activity.

The NIH AIDS prevention research agenda has also made a high priority within its NIH-sponsored portfolio of behavioral and social science on the acceptability and use of microbicides among diverse populations to ensure that these agents will be used by those at risk in order to halt the further sexual transmission of HIV and other STDs.

OBJECTIVES OF THE NIH PLAN FOR MICROBICIDE RESEARCH

The NIH comprehensive plan for microbicide development addresses the needs in microbicide research from the basic to the behavioral sciences, and is structured sequentially to include each of the different steps along the microbicides developmental pathway.

Basic biological and physiological research is of fundamental importance for the discovery and development of microbicides. There is a clear need to increase our understanding of the basic mechanisms and factors influencing HIV transmission at mucosal surfaces in order to identify multiple safe and effective strategies for blocking the early steps in the infectious process. Important areas of research under this broad aim include the identification of new viral and host targets for microbicide discovery; the determination of the first cell or tissue type that becomes infected and locally propagates HIV infection; the elucidation of the impact of microbicides on regional immune responses; studies of intercourse physiology; elucidation of the mechanism by which inflammation and/or concomitant infections influence HIV transmission; and investigations of the effects of endogenous and exogenous hormonal states on the susceptibility to infection. Emphasis should also be placed on studies of the normal vaginal and rectal ecology, since the ideal microbicide should not affect its integrity and balance. An understanding of the components of this ecosystem and their function, as well as the effect of microbicide use on them, is essential to the development of safe and effective topical microbicides.

OBJECTIVE:

- **Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal surfaces that are important for microbicide research and development in diverse populations.**

Translation of basic insights into HIV biology and pathogenesis is critical for the discovery of active agents for use as microbicides. Knowledge of the different steps required for HIV transmission and local propagation at mucosal surfaces is essential for identifying new targets for microbicides discovery and development. Likewise, an effective translation of basic insights into HIV biology and pathogenesis is also important for developing and validating relevant *in vitro* and *in vivo* models to assess safety and efficacy of candidate microbicides. Preclinical evaluation of microbicidal products should support the rationale for clinical testing in humans by providing clear evidence of activity against HIV and other STD infections in the absence of local and systemic toxicity. However, many unresolved issues such as the lack of a well-established correlation between *in vitro*, animal models, and clinical testing; insufficient knowledge about the biology of sexual transmission of HIV and other STD pathogens; the lack of optimal formulations; and insufficient knowledge on cervico-vaginal and intercourse physiology are posing a formidable challenge to rapid progress in this field and should represent the target of intense investigations by NIH-sponsored researchers.

OBJECTIVE:

- **Support the discovery, development, and preclinical evaluation of topical microbicides alone and/or in combination.**

One of the most challenging steps in the development of safe, effective microbicides is combining the active microbicidal agents into a vehicle, such as gels, creams, foaming tablets, suppositories, etc., that will enable delivery to the vagina or rectum and inactivation of infectious pathogens in the ejaculate and cervical/vaginal or rectal secretions. Microbicides can be available alone or in combination with different agents within the same product or in combination with physical barriers, such as the female condom or the cervical cap. Different active agents in the same products might act synergistically against a single pathogen or expand the range of activity against other pathogens.

Vaginal spermicides and medications have been successfully formulated and provide a framework in which to consider some of the characteristics of the formulated product. The ideal formulation should provide a uniform and durable protection at the mucosal sites without compromising the integrity of the mucosa, perturbing the local ecology, or having a systemic absorption. Formulations can have a major impact on microbicidal products' performance by either enhancing or decreasing the activity of the active agents. The field of microbicides will clearly benefit by the development of formulations that used alone without active agents would have no measurable impact on product performance and therefore could be used as true placebos in clinical trials.

The science of rectal and vaginal formulations is very complex, drawing knowledge and expertise from multiple disciplines and sectors and is a critical component of the effort to develop safe and effective microbicides.

OBJECTIVE:

- **Develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, and social sciences.**

After preclinical evaluation, all promising topical microbicides should be clinically evaluated in humans for safety and effectiveness. Safety studies (Phase I/II) are necessary to evaluate the potential for systemic absorption and toxicity as well as local toxic effects such as irritation, ulceration, itching, and burning. Irritation and ulceration of the vaginal, cervical, penile, or rectal epithelium might compromise the integrity of

mucosal tissue at those sites with a concomitant increase in the risk of HIV and STD transmission. Moreover, all adverse effects have a negative impact on the acceptability of microbicides and influence the future use of these products. Efficacy/effectiveness studies (Phase III) are then needed to assess the ability of these products to prevent HIV and/or HIV infection, depending upon the product indication. The first Phase III clinical studies of microbicides have raised problematic issues that have prompted a reevaluation of timing and methodologies for microbicides clinical trials. Several ways of streamlining this phase of development are now under consideration, including running different studies on a given product in parallel and testing multiple products in a single trial. Other important areas of research include the establishment of clinical trial sites and the necessary infrastructure to conduct those trials, especially in developing countries; the development of criteria for selecting products to be evaluated in clinical trials and for moving them through the different phases of those studies; and research into ethical and behavioral issues impacting clinical trials.

OBJECTIVE:

- **Conduct clinical studies of candidate microbicides to assess safety, acceptance, and effectiveness in reducing sexual transmission of HIV in diverse populations in domestic and international settings.**

Contributions from the behavioral and social sciences are also of fundamental importance for the development of effective and acceptable microbicides. Basic and clinical studies must be complemented by research on how people choose prevention methods—how microbicide acceptance and use affects and is affected by a variety of social, psychological, and cultural factors, including differences in human sexuality. Correct and consistent use of microbicides in the context of human sexual relationships will depend on both an optimal performance from a biomedical perspective and an appropriate acceptability profile. Acceptability studies should be performed in parallel with the development of microbicidal products, and issues related to acceptability should be addressed for both users and their partners. Although microbicide products will not be used solely by women, results from acceptability studies conducted in developed and developing countries have clearly showed that women feel an urgent need for prevention technologies that they can control and that they would be very interested in using a microbicide. These studies have also indicated that multiple formulations will be needed to meet the different needs and preferences of users. Emphasis should also be given at research aimed at identifying the social, structural, cultural, and demographic factors that affect access to and delivery of microbicides.

OBJECTIVE:

- **Conduct basic and applied behavioral and social science research to enhance microbicide development, testing, acceptability, and use domestically and internationally.**

There is a clear need to build a cadre of investigators committed to microbicide research. Toward this goal, NIH seeks to provide research training and to establish and maintain the appropriate infrastructure to conduct microbicide research, especially in developing countries. To facilitate some of these important microbicide-related activities, the plan suggests the establishment of a standing, multidisciplinary, multisectoral coordinating group with international representation to identify research gaps and funding issues, develop strategies to accelerate development of promising products, and highlight existing promising agents and products.

The encouragement of partnerships among international and national groups is exemplified in the recently formed International HIV Prevention Trial Network (HPTN) to develop and test promising nonvaccine strategies to prevent the spread of HIV. The HPTN comprises a global network of medical research centers supporting operational, data management, and laboratory core facilities. The NIH-created and -fostered network studies will focus on six key areas in prevention, and one of these key areas is microbicides designed for vaginal or rectal use, to prevent sexual transmission of HIV.

Work with national and international regulatory bodies to address regulatory issues should proceed in parallel, in order to promote the rapid development of microbicides. Collaboration with industry, as well as Government organizations and foundations, should be encouraged. At the same time, it must also be ensured that clinical studies of microbicides are undertaken at high ethical standards.

OBJECTIVE:

- **Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally.**

SCIENTIFIC PRIORITIES AND RESEARCH APPROACHES

OBJECTIVE:

Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal surfaces that are important for microbicide research and development in diverse populations.

STRATEGIES:

Basic Biological and Physiological Research Related to Microbicides

- Identify and characterize new and understudied viral and host targets important for transmission and early dissemination at the female and male genital tracts and the rectal (lower gastrointestinal [GI] tract) and oral (upper GI tract) mucosal sites that are relevant for microbicide discovery and development.
- Determine the impact of microbicides on innate and adaptive mucosal defense mechanism in the female and male genital tracts and the vaginal, oral, and rectal mucosal sites.
- Study the impact of microbicides on microbial ecology and their effects on mucosal/epithelial secretions and surfaces.
- Study intercourse physiology and discern how it relates to the transmission or acquisition of HIV and efficacy of microbicides.
- Determine the cells or tissue types that serve as portals of entry and support subsequent spread of HIV/SIV.
- Determine the role of viral phenotype/genotype/clade and delineate the relative efficiency of transmission of cell-free and cell-associated virus in secretions at the female and male genital tract and rectal and oral mucosal sites.
- Determine the mechanisms by which genital tract, oral and rectal inflammation and /or infections (including STDs) may influence HIV transmission and early dissemination.
- Investigate the effect of endogenous hormonal states (puberty, pregnancy, menopause, and menstrual cycles) and exogenous hormonal states (including oral contraceptive pill, hormonal replacement therapy) on the susceptibility of the female and male genital tract to infection with HIV.

OBJECTIVE:

Support the discovery, development, and preclinical evaluation of topical microbicides alone and/or in combination.

STRATEGIES:

Microbicide Development and Pre-Clinical Studies

- Develop, validate, and standardize specific, sensitive, and reproducible methods for quantifying HIV/simian immunodeficiency virus (SIV)/ SHIV in mucosal tissues and secretions before and after use of microbicides.
- Develop, validate, and standardize specific, sensitive, and reproducible methods for quantifying immune parameters in mucosal tissues and secretions before and after use of microbicides.
- Develop, validate, and standardize specific, sensitive, and reproducible methods for assaying antimicrobial activities *in vitro*.
- Develop and support animal models to evaluate safety and potential efficacy (including the function of frequency of use) of various topical microbicides for prevention of mucosal HIV/SIV/SHIV transmission.
- Determine the extent to which *ex vivo* and animal models are predictive of clinical efficacy.
- Integrate genomics and informatics paradigms, concepts, and methodologies (including microchip-based technology) into microbicide discovery and development research.
- Conduct preclinical studies of potential microbicides to assess immunologic and inflammatory effects, pharmacokinetics and pharmacodynamics, toxicity in the mucosal surfaces and secretions (female and male), teratogenicity, transplacental carcinogenicity, and effects on fertility.
- Develop *ex vivo* explant models of human or nonhuman primate tissue that might provide (1) a useful approach to investigate the very early events in HIV or SIV/SHIV transmission and (2) evaluate the activity and toxicity of topical microbicides.
- Improve animal models to more closely reflect the dynamics of sexual transmission in humans. Develop animal models of HIV infection that will also be able to examine the role of co-infection with STD pathogens in HIV transmission.

OBJECTIVE:

Develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, and social sciences.

STRATEGIES:

Microbicide Formulations and Modes of Delivery

- Develop formulations, dosage, and delivery systems suitable for the genitourinary and GI tracts.
- Develop chemical formulations lacking antimicrobial activity to serve as placebos.
- Identify and validate methods that improve the understanding of bioadhesion, biodispersion, retention, and distribution of microbicide formulations prior, during, and after intercourse.
- Study levels of systemic absorption from topical microbicide use.
- Develop and incorporate mechanisms to assess product acceptability in diverse populations of men and women, both within all phases of clinical studies and outside the trials setting (e.g., through focus groups).
- Understand the biologic mechanisms and physiologic changes that contribute to efficacy and safety resulting from the use of microbicide formulations, including, but not limited to, hormonal status, menstrual cycle, nature of intercourse, pregnancy, frequency of use, and foreplay.
- Develop methodology to analyze physical and chemical characteristics of compounds and formulations of microbicides and combinations of microbicides, including those derived from natural products.
- Develop methodology and supportive studies to characterize product traits, such as taste, smell, color, and tactile sense, that may affect acceptability and use of microbicides.
- Develop delivery systems that reduce or eliminate trauma to mucosal tissue.

OBJECTIVE:

Conduct clinical studies of candidate microbicides to assess safety, acceptance, and effectiveness in reducing sexual transmission of HIV in diverse populations in domestic and international settings.

STRATEGIES:

Clinical Trials of Microbicide Products

- Develop well-defined criteria for selecting products for microbicide clinical trials and for moving from Phase I through Phase III.
- Develop and evaluate improved methods to recruit and retain participants for Phase I, II, and III microbicide studies in the United States and abroad.
- Conduct research on mechanisms to improve clinical trial adherence and compliance with use requirements of products under study.
- Address ethical issues in the design and conduct of microbicide trials, including the use of placebos.
- Conduct research on ways to ensure adequate informed consent among participants in microbicide trials.
- Conduct research on the effectiveness of microbicides relative to, and in combination with, other behavioral, barrier, and therapeutic methods.
- Conduct research on the efficacy of expanding prevention choices and of hierarchical HIV prevention messages.
- Design, develop, and evaluate tools to measure product use and acceptability.
- Develop improved techniques to evaluate safety of microbicides when applied to genital and rectal mucosal and epithelial surfaces.
- Enhance understanding of the significance of clinical findings identified by current methods to evaluate safety, including evaluation of cervico-vaginal, penile, and rectal irritation.
- Study microbicide products in HIV-infected people under treatment to determine their impact on the development of drug resistance, drug-to-drug interactions, and the potential for other adverse events.

- Develop behavioral and biological markers to evaluate safety, effectiveness, and adherence to microbicides.
- Develop methods to more rapidly obtain HIV incidence rates among participants in microbicide trials.
- Support research on the development and dissemination of design alternatives to the randomized clinical trials (RCT) to evaluate safety and effectiveness of microbicides in individuals, groups, and communities.
- Design, implement, and evaluate Phase IV post-marketing surveillance studies once an effective and safe microbicide has been identified in Phase III trials.

OBJECTIVE:

Conduct basic and applied behavioral and social science research to enhance microbicide development, testing, acceptability, and use domestically and internationally.

STRATEGIES:

Social Science Research Related to Microbicides

- Support theory-building and the development of social-behavioral models of risk and protection in the context of microbicide research.
- Conduct research on how microbicide use affects and is affected by a range of psychological, social, and cultural factors such as the following:
  - differences in expression and experiences of human sexuality (including sexual orientation and sexual abuse or coercion),
  - substance use and abuse,
  - human developmental processes,
  - dynamics of intimate relationships,
  - cultural norms about gender, sexuality, fertility, and reproduction,
  - socioeconomic status, and
  - ethnicity.
- Study the social, structural (including economic), cultural, and demographic factors that affect access to and delivery of microbicides, as well as the implementation of microbicide intervention strategies in diverse populations.
- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral and social interventions related to microbicide use in different domestic and international settings and populations.
- Support domestic and international research to improve the transfer of effective microbicide interventions to and from communities, including studies of diffusion processes and the exchange of knowledge between service providers and researchers. Include post-marketing research on the maintenance of effective interventions and the generalizability of interventions among diverse populations.

- Develop improved methodologies for microbicide research, including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time, based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.

- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use in microbicide intervention studies: behavioral measures, HIV infection, and other disease outcomes such as other STDs and blood-borne diseases.

- Develop and refine mathematical models for linking microbicide interventions with a reduction in HIV and STD in different settings (i.e., as defined by levels of HIV, STDs, sexual networks, condom use).

- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal microbicide studies, including improved follow-up methodologies, methods to increase follow-up rates, and methods for dealing with subject attrition, missing data, and non-normal distributions.

- Foster the development, testing, and dissemination of design alternatives to the randomized controlled trial that permit ethical and cost-effective evaluation of microbicide interventions at the individual, group, and community levels.

- Evaluate the impact of culturally- and age-appropriate health and sexuality education in facilitating the adoption of microbicides.

- Develop provider-focused interventions to facilitate the adoption of microbicides.

OBJECTIVE:

Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally.

STRATEGIES:

Infrastructure

- Establish a standing, multidisciplinary, multisectoral coordinating group with international representation whose tasks are:
  - to identify ongoing research,
  - to identify research gaps,
  - to develop strategies to accelerate development of promising products,
  - to note existing promising compounds and products, and
  - to encourage additional research to move products into use on an urgent basis (including setting realistic and monitored time line goals).
- Establish clinical trial sites/infrastructure for Phase I, II, and III studies domestically and internationally.
- Encourage the further development of partnerships among international and national groups currently engaged in microbicide development, research, implementation, and infrastructure strengthening.
- Work with national and international regulatory bodies to address regulatory issues and structures in order to encourage more rapid development and use of microbicides.
- Identify gaps in biomedical, behavioral, ethical, clinical, and administrative training in national and international microbicide research sites, and design strategies that respond to these needs.
- Foster microbicide research training activities to encourage rapid development of national and international competitive, independent investigators (including development of mentor relationships and grant-writing skills).

- Develop strategies to strengthen training and infrastructure that will ensure that national and international microbicide research is undertaken at high ethical standards.
- Encourage development of national and international institutional capacity for microbicide research, including the enhancement of laboratory capability, data management/analysis, population-based research, research management, and physical infrastructure.
- Establish mechanisms to ensure that microbicide research is coordinated with, and informed by, other areas of HIV prevention research, including the development and evaluation of physical barrier methods.
- Address obstacles to microbicide research, including administrative and other barriers to international research.
- Encourage collaboration with national and international corporate enterprises, governmental and nongovernmental organizations, foundations, training institutions, and multilateral organizations involved in or concerned with microbicide research and training.
- Develop training and institutional strengthening strategies to involve national and international communities in the planning and undertaking of international microbicide research. This includes building and maintaining sites for population-based research and assuring that communities involved in research will be prepared to benefit from the research results.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2003 OAR Planning Group for Microbicides

FY 2003 MICROBICIDES PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
AVEG/HVTN	AIDS Vaccine Evaluation Group/HIV Vaccine Trials Network
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CBO	community-based organizations
CDC	Centers for Disease Control and Prevention
CFAR	Centers for AIDS Research
CIPRA	Comprehensive International Programs in Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocytes
DC	dendritic cell
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GI	gastrointestinal

GLP/GMP	good laboratory practices/good manufacturing production
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Unviersities
HBV	hepatitis B virus
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpes virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IHS	Indian Health Service
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpes virus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MCT	mother-to-child transmission
MDR-TB	multiple drug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organizations

NHL	non-Hodgkin's lymphoma
NHP	non-human primate
NIH	National Institutes of Health
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PHS	Public Health Service
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trials
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	Structured Treatment Interruption
TB	tuberculosis
TI	treatment interruption
UNAIDS	United Nations Joint Programme on AIDS
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

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